Advanced Pharmaceutical Technology

Transdermal Drug Delivery

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Introduction

- Human skin is a formidable barrier
- Delivering drugs to and through the skin can be advantageous by avoiding first-pass metabolism
- Topical drug delivery treats a local disorder and the drug is retained within the skin
- Transdermal drug delivery relies on the skin to deliver the drug to the systemic circulation

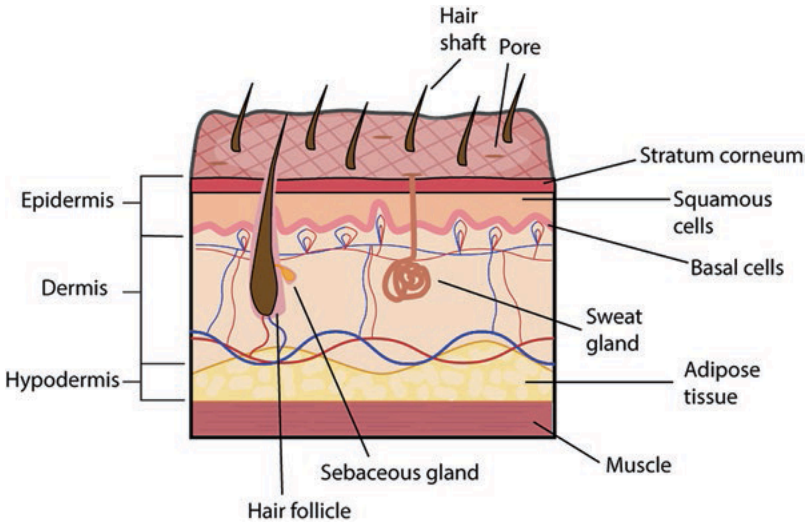
Introduction

- Numerous formulation options are available for topical drug delivery, most common of which are creams, gels, lotions and ointments
- Patches, of varying complexities, are the most common transdermal drug delivery systems
- Transdermal and topical drug delivery can be enhanced by some formulation strategies, such as using penetration enhancers
- Drug delivery through the nail is even more challenging than delivering drugs through intact skin (Why?)

Structure of the skin

- Skin is a complex multi-layered membrane divided histologically into the stratum corneum (the outer layer), the epidermis, and the dermis
- Blood capillaries and nerve fibers rise from the subcutaneous fat into the dermis and up to the epidermis
- Skin appendages such as the sebaceous glands, sweat glands, and hair follicles originate in the dermis and subcutaneous layers and rise to the skin's surface

Structure of the skin



Structure of the skin

- The outermost layer, the stratum corneum, provides the main barrier to drug delivery
- The stratum corneum is around 10 µm thick when dry (although it can swell to several times this when wet)
- The stratum corneum is thinnest on the lips and eyelids and thickest on the load-bearing areas of the body
- The appendages (hair follicles, sebaceous and sweat glands) can act as 'short cuts' through which molecules can pass across the stratum corneum barrier
- But they occupy a relatively small surface area and the ducts are seldom empty

Drug diffusion through the skin

- The ability of a drug to diffuse out of a formulation that is applied to the skin, and then across the skin, is dependent upon several factors, including:
  - The intrinsic properties of a drug
  - The formulation composition
  - The excipients in the formulation that may interact/disrupt the skin barrier
- Drugs suitable for transdermal drug delivery usually have a molecular weight < 500 Da, Log P between 1 – 4 and an effective daily dose of < 10 mg/day

Drug diffusion through the skin

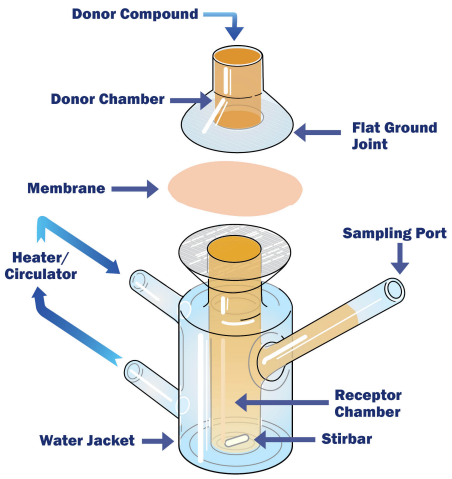
- Drug diffusion through the skin at steady state can be described using Fick's first law:

$$J = D.P.(C_1-C_2)/h$$

  - Where:
    - J is the flux (dM/dt) of the drug through the membrane (skin)
    - D is the diffusion coefficient in the skin
    - h is the diffusional path length
    - P is the partition coefficient between the skin and the vehicle
    - C_1 and C_2 are the concentrations in the two compartments (C_2 may be neglected if sink condition is applied)

Drug diffusion through the skin

- Percutaneous absorption of a drug is commonly tested in vitro using a Franz diffusion cell



Enhancing drug penetration through skin

- Based on Fick's law, there are three main mechanisms for enhancing diffusion:
  1. Increasing D
     - Occlusion
     - Increasing skin temperature
     - Using chemical penetration enhancers
  2. Increasing P
     - The drug should have a greater affinity to the skin than the vehicle
  3. Increasing the degree of drug saturation in the vehicle (C_1)
     - Increasing the drug concentration in the vehicle or decreasing its solubility in the vehicle (supersaturated solution)

Penetration enhancers

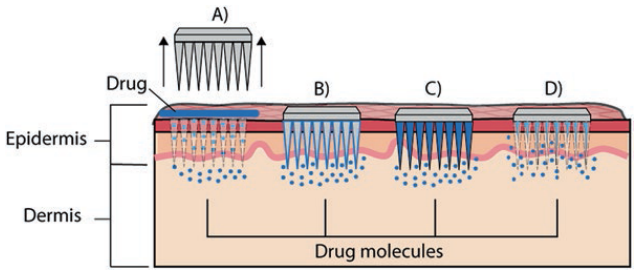
- **Chemical** penetration enhancers include:
  - Surfactants (such as polysorbates)
  - Fatty acids/esters (such as oleic acid)
  - Terpenes (such as limonene)
  - Solvents (DMSO and ethanol)
- Surfactants can increase the diffusion coefficient by solubilizing or extracting lipids from the stratum corneum
- Fatty acids with bulky polar heads can increase lipid bilayer fluidity

Penetration enhancers

- Skin uptake of solvents such as propylene glycol, ethanol, and transcutol can increase permeation by increasing drug solubility in the skin
- Use of chemical penetration enhancers is limited by their tendency to cause skin irritation
- They demonstrate only limited success in the permeation enhancement of large drugs like peptides and proteins

Penetration enhancers

- Physical agents such as microneedles, heat, thermal ablation, iontophoresis and ultrasound can produce a greater magnitude of skin permeability enhancement than the chemical penetration enhancers
- These physical methods can permit the permeation of large, polar and charged drugs such as peptides, proteins and oligonucleotides



A) Solid microneedles
B) Drug-coated microneedles
C) Hollow microneedles
D) Dissolvable microneedles

Table 18.4 Physical methods to enhance the permeability of the skin

Method	Description	Clinical/preclinical applications
Heat	Separate compartment of proprietary powder mixture reacts with oxygen when the patch is opened to generate heat to warm the skin	Lidocaine/tetracaine controlled heat-assisted drug delivery patch (Synera)
Thermal ablation	Heating of the skin surface to hundreds of degrees for a very short period of time to create microchannels in the stratum corneum	Parathyroid hormone, interferon-alfa, hepatitis B antigen, erythropoietin, teriparatide
Microneedles	Hollow or solid device that is long enough to create a channel for drug solution through stratum corneum but short enough not to excite nerve endings in the dermis	Parathyroid hormone, insulin, immunoglobulin G, desmopressin, human growth hormone, influenza vaccine, hepatitis B vaccine
Iontophoresis	Continuous electric current to drive charged drug molecules across the skin	Fentanyl, lidocaine, zolmitriptan, parathyroid hormone, LHRH, insulin
Electroporation	Use of short, high voltage electrical pulses to create transient pore-like disruptions in the stratum corneum	Salmon calcitonin
Sonophoresis	Ultrasound applied to the skin to produce cavitational bubbles which oscillate and disrupt stratum corneum structure	Insulin, heparin, interferon gamma, erythropoietin

Transdermal patches

- Patches are the most common formulation for transdermal drug delivery
- **Advantages:**
  1. Avoidance of first-pass metabolism
  2. Improved patient compliance
  3. Decreased fluctuations of drug levels in the blood through controlled release
  4. When necessary the patient or caregiver can terminate drug action relatively quickly by removing the device from the skin
- Examples: clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, estradiol, testosterone, and scopalamine

Characteristics of transdermal patches

1. One dose in a manageable size unit
   - The dose of a transdermal patch is determined by the surface area of skin in contact with the patch. Thus as the size of patch area increases, the dose delivered will increase
2. Comfort
   - The occlusiveness of transdermal patches, in addition to the chemical irritant properties of drugs and adhesives, contribute to the high incidence of skin reactions to the devices. Fortunately most reactions are mild
3. Stability
   - In general transdermal patches provide good stability

Characteristics of transdermal patches

4. Convenience/ease of use
   - Unit dose packaging enables the patient to easily carry the devices
   - Transdermal products allow infrequent (daily, weekly) dosing that facilitates patient compliance
5. Drug release
   - Drug is released from patches by diffusion and typically follows zero-order kinetics
   - The dose of drug in a transdermal patch exceeds the amount delivered in order to provide consistent drug release over the period of application
   - All transdermal patches are constructed with occlusive backing that prevents the loss of water resulting in hydration and swelling of the stratum corneum barrier, significantly increasing drug absorption.

Design of transdermal patches

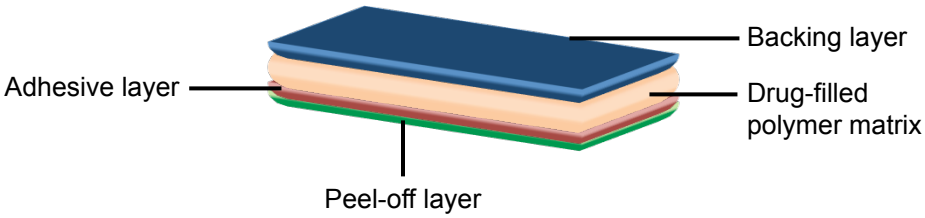
- Transdermal patches can be classified into two categories, based upon their design:
  1. Matrix-type (drug-in-polymer or drug-in-adhesive)
  2. Reservoir-type

1. Matrix-type patches:

- Consist of an impermeable backing layer, a solid drug-polymer matrix layer, and an adhesive layer. In some cases, the adhesive may be combined with the drug-polymer matrix (drug-in-adhesive)

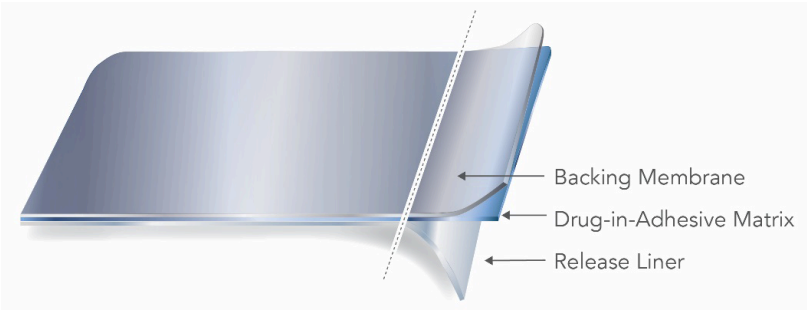
Matrix-type patches

- Drug-in-matrix patches:
  - Drug is embedded in a polymer matrix to control and prolong its release
  - More drug may be incorporated
  - Typically produced as large sheets that are later cut into smaller patches



Matrix-type patches

- Drug-in-adhesive patches:
  - Easiest to manufacture but have limited drug loading
  - e.g. nicotine and glyceryl trinitrate patches



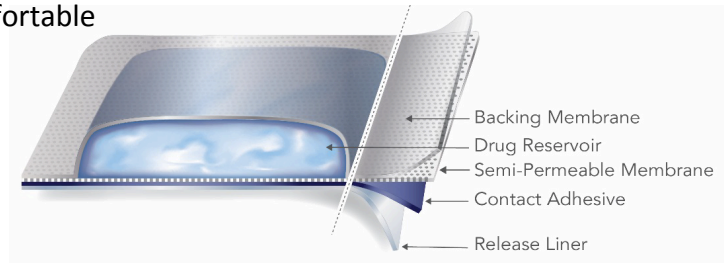
Matrix-type patches

- Drug release from matrix-type patches follows Fick's law of diffusion
- Flux (J) is not rate-controlled by the patch, rather it is controlled by the skin barrier
- The matrix is formulated with an excess of drug so that the flux will remain constant (zero-order release) for the duration of the patch use
- Because the matrix is monolithic this patch design has low dose dumping potential
- However, if the permeability of the drug across the skin is increased, as in the case of damaged or compromised skin, then the release of drug from the polymer matrix will also be increased

Design of transdermal patches

2. Membrane-controlled (reservoir) patches

- Contain an excess of the drug, usually in liquid or gel form; a rate-controlling membrane; and backing, adhesive, and protecting layers
- As long as the drug solution in the reservoir remains saturated, the rate of drug release through the controlling membrane remains constant (zero-order)
- They are bulkier than matrix-type patches and less comfortable



Other transdermal delivery systems

- Semi-solid preparations (gels and ointments) can also be used for transdermal delivery
- Typically contain penetration enhancers in the formulation
- While the dose is less exact than delivered by a patch, the semisolids may be a good choice for patients who experience allergic reactions to components of transdermal patches

Other transdermal delivery systems

- Regional transdermal systems are available as patches, and as creams and gels that may be applied to the affected limb multiple times per day
- Regional transdermal systems do not differ in design from the systemic transdermal dosage forms but are intended to be applied to the affected body part
- This method of use confines the absorption of drug to the affected area only
- Regional delivery may be used with drugs that have a daily oral dose larger than 20 mg and for NSAIDS as an approach to reduce gastrointestinal side effects

Quality evaluation of transdermal products

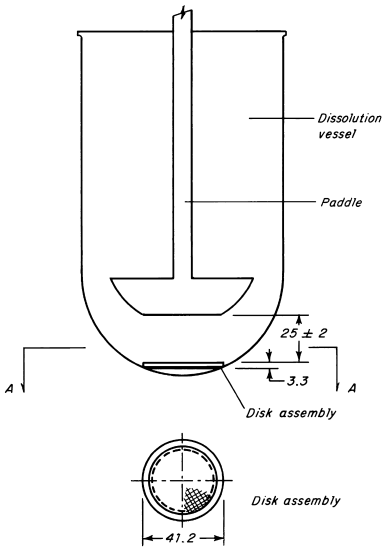
1. Physical evaluation: Film thickness, % flatness, folding endurance, tensile strength/shear strength
2. Uniformity of dosage units (weight and content)
3. Adhesive test: peel adhesion test, tack test
4. Leak test
5. In vitro drug release/skin permeation studies
6. In vivo evaluation
7. Skin irritation studies

Quality evaluation of transdermal products

- There are a variety of methods to evaluate the drug release rate of transdermal delivery systems in vitro. These methods include the following:
  1. The transdermal system is placed in the disk at the bottom of the USP Dissolution Apparatus 5 (paddle over disk) and suspended in a suitable medium at 32°C.
  2. The transdermal system is placed between the receptor and donor compartment of a Franz diffusion cell with the releasing surface facing a suitable fluid in the receptor compartment

USP apparatus 5 for transdermal patches

- The disk assembly for holding the transdermal system is designed to minimize any dead volume between the disk assembly and the bottom of the vessel
- The disk assembly is positioned so that the release surface is parallel with the bottom of the paddle blade



Bioequivalence of transdermal products

- To receive approval for a generic transdermal drug product, the manufacturer must establish that its product has the same active ingredient, strength, site of administration, adhesion, local irritation, sensitization and conditions of use
- In addition, the manufacturer has to show and that the active ingredient is absorbed into the blood stream to the same extent and at the same rate as the innovator product
- Note that reservoir patches may be pharmaceutically and bioequivalent to matrix or drug in adhesive matrix patches and therefore interchangeable

Case studies

- Indulekha, S., et al. *Thermoresponsive polymeric gel as an on-demand transdermal drug delivery system for pain management*. Mater. Sci. Eng. C 2016, 62, 113-122
- Ameen, D., et al. *Transdermal delivery of dimethyl fumarate for Alzheimer's disease: Effect of penetration enhancers*. Int. J. Pharm. 2017, 529, 465-473
- Shaker, D.S., et al. *Boosting transdermal delivery of atorvastatin calcium via o/w nanoemulsifying system: Two-step optimization, ex vivo and in vivo evaluation*. Int. J. Pharm. 2020, 119073